orientation, wherein the fusion protein is optionally linked to a fusion partner, and wherein the fusion protein is in admixture with a pharmaceutically acceptable excipient.

Please cancel Claims 37 and 38.

Please amend Claim 39 as follows:

39. (Amended) The composition as claimed in Claim 32, wherein the fusion partner comprises between 100-130 amino acids from the N-terminal of Haemophilus influenza B protein D.

Please add the following new claim:

78. (New) The composition as claimed in Claim 32, wherein the fusion partner comprises at least the N-terminal third of Haemophilus influenzae B protein D.

REMARKS

Claims 32-54 are in this application. Claims 55-77 are withdrawn from consideration. Applicants hereby cancel Claims 55-77 and reserve the right to prosecute these claims in a divisional application. Applicants acknowledge entry of the amendment filed on April 17, 2002.

Claims 37 and 38 stand rejected under 35 U.S.C. § 112, first paragraph as lacking written description for use of the phrase "immunogenic derivatives thereof". In order to advance prosecution in this case, Applicants have cancelled Claims 37 and 38, amended Claim 39 to correct its dependency, and added new Claim 78 to address the Examiners concerns. Support for new Claim 78 may be found in the specification at page 1, line 33 to page 2, line 2.

Claims 32-54 stand rejected under 35 U.S.C. § 112, first paragraph as not enabling for "mutants" and "immunogenic derivatives" of Nef-Tat and fusion partner-Nef-Tat as set out in SEQ ID Nos: 12, 13, 16, 17, 20, 21, 23 and 24. The Examiner's rejection is essentially an objection to the phrases "mutants thereof" and "immunogenic dervivatives thereof", arguing that the claims are not enabled throughout their breadth under In re Wands. The Examiner asserts that "[t]he amount of direction or guidance present in the specification is insufficient to allow the ordinary artisan to make mutations in the sequences and be able to determine at what point the mutations in the sequences of Tat or Nef will fall outside the claimed immunogenic composition or 'mutant thereof' or 'immunogenic derivatives thereof'".

Importantly, the Examiner also states that "[t]he specification provides no measurable function that can be used as a guide when making 'mutants thereof' or 'immunogenic derivatives thereof'". Applicants respectfully disagree, and assert that the specification provides sufficient guidance so that one skilled in the art can make any mutant of Tat or Nef and determine whether it is immunogenic (Applicants also point out that entrance of the amendment filed April 17, 2002 (Paper No. 17) and cancellation of Claims 37 and 38 herein eliminated the phrase "immunogenic derivatives thereof" from the claims). Example 6, starting at page 24 of the instant specification, describes several means for measuring immunogenicity that one skilled in the art may use to determine whether a fusion protein comprising a particular mutant of Nef or Tat is immunogenic. Accordingly, the specification provides a "measurable function" that can be used as a guide when making mutants of Tat and Nef. Since the claims are limited to "immunogenic compositions", and since the specification provides several means for assessing the immunogenicity of the instant compositions, Applicants respectfully assert that the full breadth of the pending claims is enabled.

Furthermore, the Examiner's citation of several anecdotal references concerning specific proteins would not be persuasive to one skilled in this art. The person skilled in this field is equipped with significant knowledge and instrumentation to be able to predict with reasonable certainty mutations which will be tolerated by the recited HIV proteins. Coupled with the availability of a method for assessing the impact on immunogenicity of those mutations as set forth in the instant specification, the amount of experimentation required to define, synthesize and test immunogenic mutants is not undue but routine in this art. Regarding the Examiner's assertion that an indefinite number of mutations can be made, one skilled in the art is well aware of the nature and structure of HIV Nef and Tat proteins, and will thus be cognizant of maintenance of the essential nature of these proteins. Moreover, it is apparent from the specification and claims that at least one utility of the current invention is the induction of an immune response that will ameliorate a condition caused by the HIV virus, the causative agent of AIDs. Accordingly, one skilled in this art will thus limit any mutations in Nef and/or Tat to those which are still able to induce an immune response that recognizes the native Nef and/or Tat proteins. For all of the above reasons, Applicants respectfully assert that the instant specification and claims are reasonably enabled under a Wands analysis, and that the § 112, first paragraph rejection should be withdrawn.

Claims 32-53 stand rejected under 35 U.S.C. § 112, second paragraph as indefinite. The Examiner states that it is unclear whether Applicants intend any particular order of the Nef-Tat or Tat-Nef orientation in Claim 32. Applicants assert that claimed invention is an immunogenic composition drawn to fusion between HIV Nef and Tat proteins, or derivatives thereof, wherein the fusion protein is optionally fused to an additional protein. Orientation of the components of the fusion protein relative to each other is not meant to be in any way limited. Applicants herein amend Claim 32 to address the Examiner's concerns, and respectfully request withdrawal of the 35 U.S.C. § 112, second paragraph rejection.

Claims 32-54 stand rejected under 35 U.S.C. § 103(a) as obvious over Schluesener and Hinkula. In addition, Claim 35 is rejected over Schluesener and Hinkula and further in view of Gayner, Claims 50-53 are rejected over Schluesener and Hinkula and further in view of Berman, and Claims 37-39 are rejected over Schluesener and Hinkula and further in view of Forsgren. Applicants respectfully traverse.

The Schluesener reference is not relevant to the instant invention, and would be viewed by one skilled in this art as teaching away from the instant invention. A careful reading of Schluesener indicates that the author used a portion of the HIV-1 Tat protein as a means of targeting autoimmune T-cell epitopes for cellular uptake and induction of tolerance to the fused epitopes. That is, Schluesener fused T-cell epitopes to the HIV-1 Tat peptide for the purpose of preventing the induction of an immune response, in this case an autoimmune response to the fused epitopes. Therefore, any composition disclosed in Schluesener is tolerogenic, not immunogenic. In contrast to the Examiner's comment, the fusion combination to HIV Tat as taught by Schluesener does not improve immunogenicity of the fused epitopes but instead induces immune tolerance against the fused epitopes (tolerance has been defined as the acquired inability of an individual to express specific cell-mediated or humoral immunity to a molecule or antigenic determinant to which it would otherwise respond; see Benacerraf, B. and Unanue, E., Textbook of Immunology 166 (1979)). At page 258, column 2 of the Schluesener reference, the author indicates that the effects of Tat-mediated targeting of proteins on the immune system are unknown, and thus "might effectively induce immune responses or could potentially be used to tolerize the immune response." The data presented by Schluesener would lead one skilled in the art conclude that of the choices articulated by Schluesener at column 2 of page 258, the latter (i.e., tolerance) seems likely. Thus, one skilled in this art would be led away from using Tat-mediated delivery for induction of an immune response to a fused epitope: Schluesener is silent on the

use of Tat as anything more than a means for targeting of epitopes for the purpose of tolerization. There is no teaching or suggestion in Schluesener to use Tat to facilitate the induction of an immune response to Tat or any fused epitope or antigen.

Hinkula et al. demonstrate that genes encoding the HIV regulatory proteins Nef, Rev and Tat, when administered to experimental inbred rodents, can induce humoral and cellular immune responses to the encoded antigens. Although some F1 animals received a combination of plasmids, in no case were the plasmids constructed for secretion of the cDNA product (see Hinkula et al., page 5529, column 1), and in no case were any of the individual regulatory proteins expressed as fusion proteins, either fused to one another or to any other protein. Applicants respectfully assert that Hinkula's intracellular, DNA-mediated expression of individual, unfused HIV regulatory genes would not motivate one skilled in this art to produce a fusion protein comprising Tat and Nef and to administer the fusion protein in admixture with an excipient, let alone with an adjuvant, for the purpose of inducing an immune response. Moreover, in view of the teaching of the Schluesener reference cited by the Examiner, and the ability of Tat fusions to induce immunological tolerance, one skilled in this art would avoid such fusions. There is simply not motivation in Hinkula et al. to make such fusions; Hinkula et al. merely demonstrate that intracellular expression of certain HIV regulatory genes results in induction of some humoral and/or cellular immune responses. Especially in view of the Schluesener reference, Hinkula et al., either alone or in combination with the other cited references, does not teach or suggest the instant invention. Accordingly, neither of the primary references cited by the Examiner, taken alone or together, teach or suggest the instant invention.

Gaynor et al. are concerned with transdominant Tat mutants as therapeutic agents to inhibit wild-type Tat function in infected cells. Gaynor does nothing to cure the defects of the primary reference; i.e., Gaynor does not teach or suggest fusing Tat or mutants thereof to Nef or mutants thereof for any purpose, let alone to form an immunogenic composition, and there is no motivation to combine Gaynor with the primary references to reach the instant invention claimed in Claim 35.

As admitted by the Examiner, Berman does not teach or suggest the instant fusion proteins comprising HIV Nef and Tat. Accordingly, like Gaynor, Berman does not cure the defects of the primary references.

Finally, as admitted by the Examiner, Forsgren does not teach or suggest the instant fusion proteins comprising HIV Nef and Tat. Accordingly, like Gaynor and Berman, Forsgren does not cure the defects of the primary references.

For all of the above reasons, Applicants respectfully assert that the pending claims are not obvious in view of any of the cited references, either taken alone or in any combination, and respectfully request withdrawal of the 35 U.S.C. § 103(a) rejection.

Attached hereto is a marked-up version of the changes made to the claims by the instant amendment. The attached pages is captioned "Version with markings to show changes made."

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

32. (Amended) An immunogenic composition which comprises a fusion protein comprising[:
(a)] an HIV Tat protein or a mutant thereof linked to an HIV Nef protein or a mutant thereof[; or
(b) an HIV Nef protein or a mutant thereof linked to an HIV Tat protein a mutant thereof; or
(c) an HIV Nef protein or a mutant thereof linked to an HIV Tat protein a mutant thereof and], wherein the HIV Tat and Nef proteins or mutants thereof are linked in any orientation, wherein the fusion protein is optionally linked to a fusion partner, and wherein the fusion protein is in admixture with a pharmaceutically acceptable excipient.

39. (Amended) [A] The composition as claimed in Claim [38] 32, wherein the fusion partner comprises between 100-130 amino acids from the N-terminal of Haemophilus influenza B protein D.